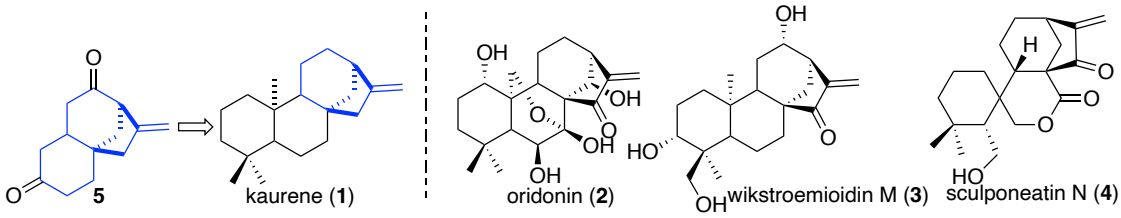
Final Report
Organo-Photoredox Catalysis in Total Synthesis of Terpenoids

Introduction

Plants of the *Isodon* genus[1] have been a rich source of terpenoid natural products, valued both for the diversity and complexity of their chemical structures, and for their broad range of biological activities. Even the traditional Chinese folk medicine has relied on this family of herbs, especially on Donglingcao (*Isodon rubescence*), to treat a wide spectrum of maladies, including, but not limited to, cancer, inflammation, malaria, bacterial infections of the lung or gut, and pneumonia. Furthermore, the curative properties of the plants of *Isodon japonica* and *Isodon trichocarpa* are so respected in Japan that, in fact, these herbs are known as ”enmei-so” or “grass effective for the prolongation of human life.”
Up until now, more than 600 diterpenoids have been isolated from *Isodons*, which could be classified into 11 groups including five subgroups. Although a cursory look of their remarkable diverse array of polycyclic structure might hide their biogenetic origin (Scheme 1), all of them are biosynthetsized from kaurene (**1**) in oxidative and fragmentative pathways.



Scheme 1. The kaurane core and selected Isodon terpenoids.

As many of these Isodon terpenoids exert a strong antitumor activity[2] along with relatively low toxicity, there is an ever-growing interest in Isodon terpenoids and oridonin (**2**) has become a ”hot molecule” in recent years.[3] Accordingly, the potent and often highly selective antitumor activity, coupled with the structural diversity of the *Isodon* terpenoids, have triggered a number of research groups to start synthetic programs to accomplish the total synthesis of kaurene terpenoids. As a result, various synthetic approach has been published in top journals reflecting both the medicinal importance and inherent synthetic challenges of these natural products.[4] Importantly, many synthetic inventions have been developed to overcome key challenges associated with the interwoven and sterically congested ring systems of kaurenes. An additional element of daunting challenges is the stereoselective construction of quaternary carbon stereocenters of which these terpenoids are richly endowed.

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[1] Sun, H.-D.; Huang, S.-X.; Han, Q.-B. *Nat. Prod. Rep.* **2006**, *23*, 673.
[2] (a) Leung, C.-H.; Grill, S. P.; Lam, W.; Gao, W.; Sun, H.-D.; Cheng, Y.-C. *Mol. Pharm.* **2006**, *70*, 1946. (b) Hou, J.-K.; Huang, Y.; He, W.; Yan, Z.-W.; Fan, L.; Liu, M.-H.; Xiao, W.-L.; Sun, H.-D.; Chen, G.-Q. *Cell Death Dis.* **2014**, *5*, 1400.
[3] Liu, X., Xu, J., Zhou, J., Shena, Q. *Genes Dis.* **2021**, *8*, 448.
[4] (a) Li, W., Wang, J., Ma, D. *Prog. Chem.* **2019**, 31, 1460. (b) Zhao, X., Cacherat, B.,Hu, Q., Ma, D. *Nat. Prod. Rep.* **2022**, *39*, 119. (c) Ao, J., Sun, C., Chen, B., Yu, N., & Liang, G. Angew. Chem. Int. Ed. 2022, 61, e20211448.

Despite these apparent advances, the synthetic pathways are still not concise and practical to provide target compounds in useful quantities for further biological developments.

Initiative

Whereas *Isodon* terpenoids have recently garnered increasing interest owing to their promising anti-cancer properties, their further development is hampered by the lack of efficient and general synthetic strategy to provide them or their structural analogs in rapid, scalable, and efficient manner. Our primary aim was to find a general and divergent strategy for the synthesis of *ent*-kauranes which would allow the construction of various derivatives. After structure pattern analysis, we identified a "privileged intermediate" **5** for a strategically different, unprecedented approach which aims to build up the shared core-structure of kauranes from the structurally most complex bicyclooctane fragment. Furthermore, this intermediate was expected to serve as basis for a synthetic network for rapid access to various *Isodon* terpenoids. Beside modern organocatalytic asymmetric developments, we took a hypothesis-driven visible light photo-redox C-C bond formation approach towards synthesis of these highly advanced intermediates with a hope to profoundly boost and facilitate lead structure developments among *Isodon* terpenoids.

Results

The choice of the strategy of any total synthesis lies on the availability of the starting materials, selectivity of the reactions and the yields of the reactions. With this general initiative in our mind, a retro-synthetic analysis was conducted which suggested cyclohexenone derivatives **6a-c** with a quaternary stereocenter (Scheme 2). Recently, the challenging enantioselective synthesis of such derivatives were executed with high enantioselectivities via organocatalytic Robinson annulation.[5] This general building block has several structural features which could be exploited for our synthetic initiative. The role of the quaternary stereocenter is dual: it can control further diastereoselective transformations and inhibits olefin migration. Accordingly, a nucleophilic addition to the highly active π-system does not compete with γ-deprotonation which would eliminate the original reactivity. In a parallel project, we demonstrated the broad utility of such type of chiral building block in total synthesis. In 2020, we published two papers[6] which exploited this type of cyclohexenone core for the concise synthesis of various Aspidospermane alkaloids (see later as “spin-off activities”).
As a first synthetic endeavor, various cyclohexenones **6a-c** were synthesized having either allylic or acetylenic substituents at the quaternary stereocentrum (Scheme 2). Then [3.2.1]bicyclooctane derivatives **7a,b** were targeted via Toyota-type palladium catalyzed cyclo-alkenylation[7] of allyl derivatives **6a,b**. After extensive optimalization, we managed to synthesize the desired compounds in a reproducible and scalable way. Thus, we could scale-up not only the organocatalytic, but also the subsequent

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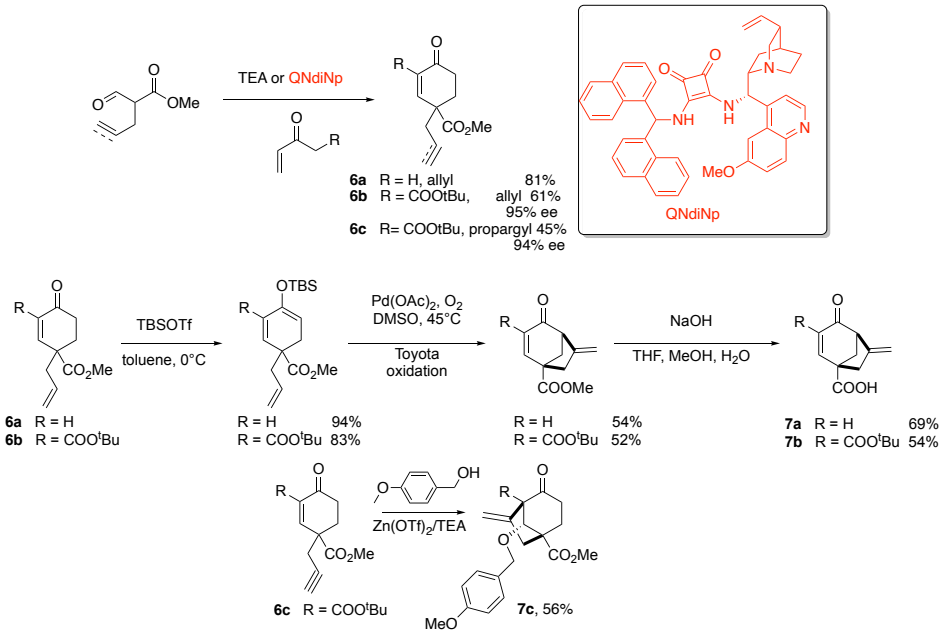
[5] Berkes, B., Ozsváth, K., Molnár, L., Gáti, T., Holczbauer, T., Kardos, Gy., Soós T. *Chem. Eur. J.* **2016**, *22*, 18101.
[6] Varga, S., Angyal, P., Martin, G. Egyed, O., Holczbauer, T., Soós, T. *Angew. Chem Int. Ed.* **2020**, *59*, 13547. (b) Martin, G., Angyal, P., Egyed, O., Varga, S., Soós, T. *Org. Lett.* **2020**, *22*, 4675.
[7] Toyota, M.; Wada, T.; Ihara, M. *J. Org. Chem.* **2000**, *65*, 4565.

organometallic step and had a rapid access to bicylooctanes in multi-dekagramm scales. Besides Toyota-type coupling, we also investigated the applicability of Conia-ene type cyclization using propargyl derivative **6c**. We envisioned that the required β-oxo carboxylic nucleophile for the Conia-ene reaction[8] can be generated in a reversible Michael addition reaction on the electron-deficient olefinic group. Gratifyingly, after some optimization, we could develop a unique Michael-Conia cascade process which delivered an alkoxylated derivative. Importantly, this alternative method allows the introduction of O-based functionality in a rather challenging position (e.g. in oridonine) which is a common structural feature in many Isodon terpenoids.

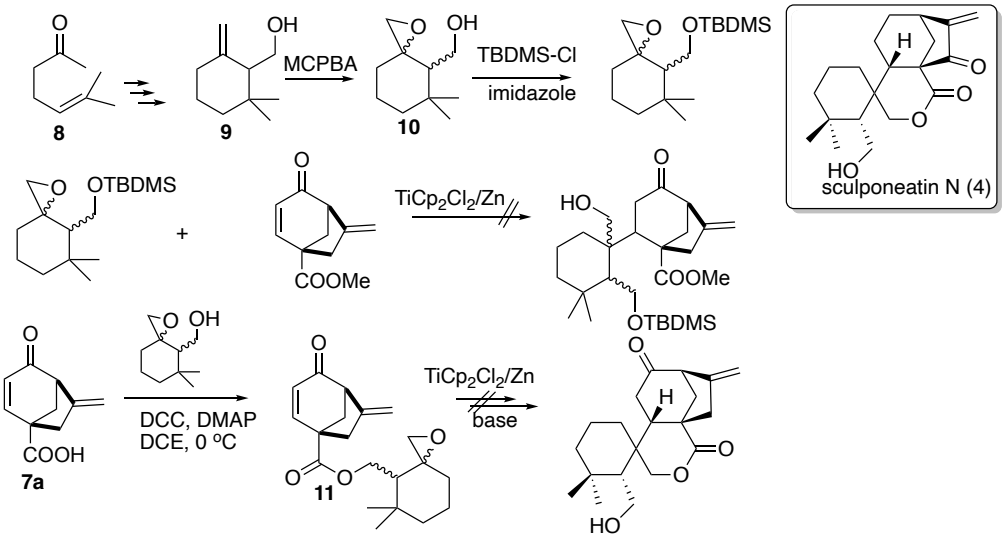


Scheme 2. Syntheses of bicyclooctane core

Having in hand scalable and reliable routes toward variously decorated bicyclooctanes, we first probed this building block in classical radical cyclization synthetic pathways to produce spirolactones (Scheme 3). More specifically, the advanced building block x has been probed to construct the targeted natural product sculponeatin N (**4**). Unfortunately, the originally proposed (Scheme 5 in the proposal) photo-redox mediated decarboxylative pathway failed to provide the required C-C connectivity. Thus, a similar radical based approach was investigated. We envisioned that a Ti(III) initiated radical opening of epoxide might be a enabling alternative to generate that spirocyclic structure of the sculponeatine N (**4**). Thus, starting from 6-methyl-hept-5-en-2-on (**8**), we have developed a five-step synthetic route to γ-cyclogeraniol (**9**) which was converted to epoxy derivative **10**. Then an intermolecular redox coupling was probed using an *in situ* generated Ti(III) reagent, using Nugent-Rajanbabu reagent[9] and Zn. Unfortunately, no redox coupling was detected, only the dimerization of the cyclohexanone occurred. Thus, we tried to intramolecularize this process after the synthesis of ester **11**. Unfortunately, after several experimentations,

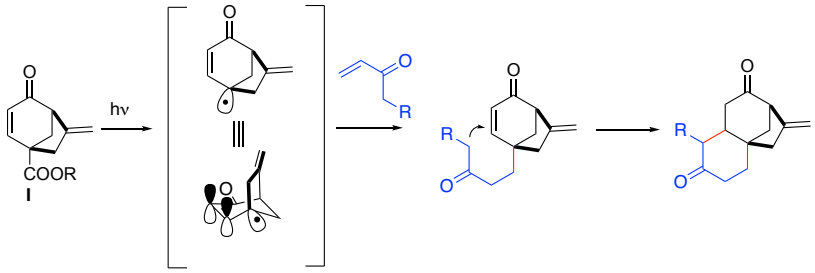
[8] Conia, J. M., Le Perchec, P. *Synthesis* **1975**, 1.
[9] Nugent, W. A., RajanBabu, T. V. *J. Am. Chem. Soc.* **1988**, *110*, 8561.

we cannot accomplish the synthesis of the target compound owing to extensive side reactions and decompositions.



Scheme 3. Synthetic studies toward kaurene spirolactones.

This synthetic dead-end triggered us to pursue the alternative "iso-Diels-Alder" synthetic plan outlined in our grant proposal (Scheme 4). We anticipated that an unprecedented annulation can be realized on a bridgehead position in a stepwise manner. More specifically, we expected the formation of a bridgehead radical in a photoredox mediated reaction from carboxylic acid **I**. Owing to the strained, bicyclic structure, the transiently generated radical is non-conjugated, orthogonal to the electron-deficient olefinic bond, allowing to achieve a selective Giese-type reaction at that position. After the Giese-type C-C bond formation, further radical or ionic processes were envisioned to secure the formal 4+2 annulation.

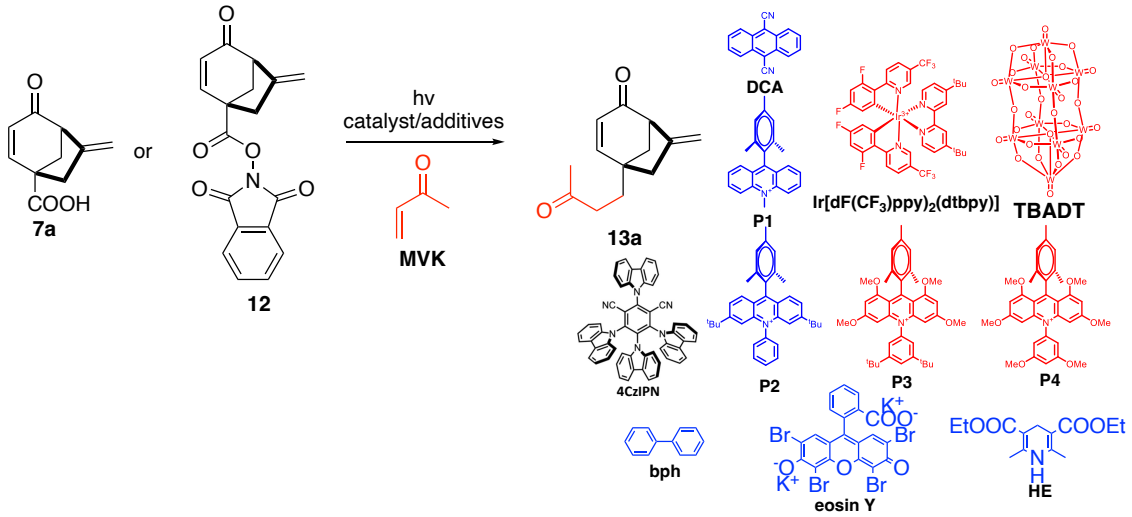


Scheme 4. Envisioned iso-Diels-Alder strategy.

As a first and critical step, a photo-redox mediated Giese-type coupling was probed between methyl-vinyl ketone **MVK** and the free carboxylic acid **7a** or its redox active ester derivative **12** (Scheme 5). We synthesized various Fukuzumi-type catalysts **P1-P4**[10] and screened them along with other commercially available catalysts. To our delight, we could observe the formation of the desired coupled product **13a**. Most importantly, we found that application of **bph** additive was critical to achieve yields (entry 6 vs 7). Interestingly, most of the known and broadly utilized organic and organometallic photo-redox catalysts failed to deliver the required product. Further optimization in the structure of the Fukuzumi catalyst (**P2**) resulted in a significantly

[10] Joshi-Pangu, A., Lévesque, F., Roth, H. G., Oliver, S. F., Campeau, L.-C., Nicewicz, D., DiRocco, D. A. *J. Org. Chem.* **2016**, *81*, 7244.

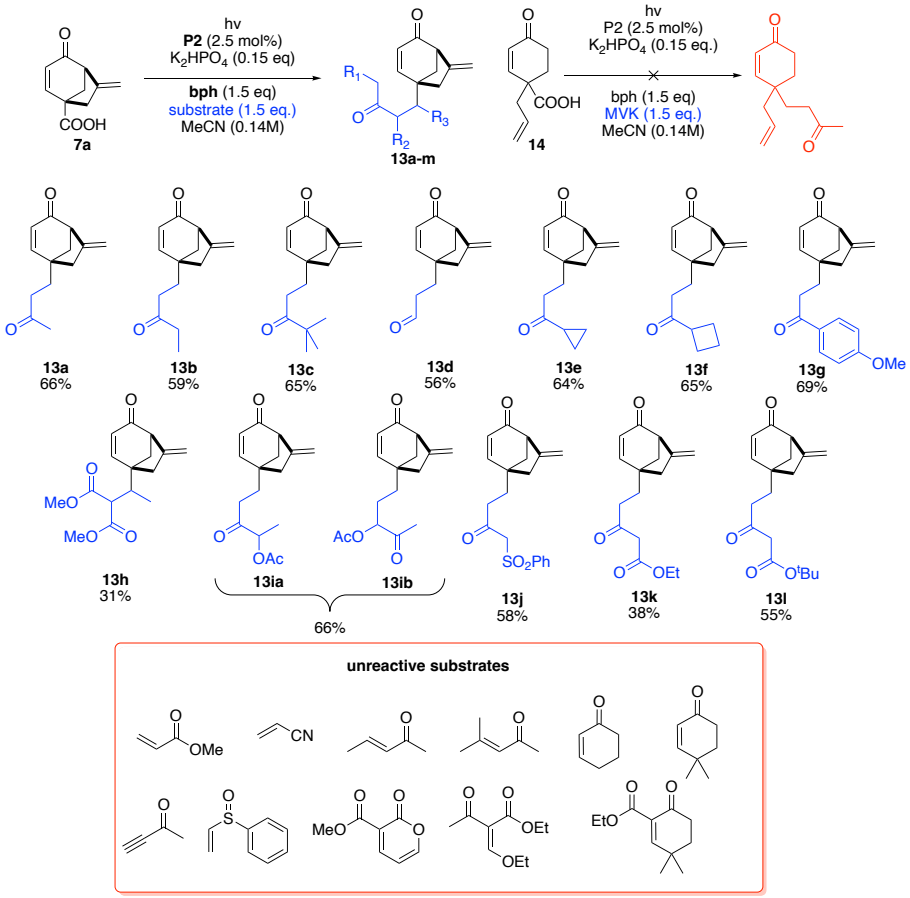
faster and more efficient Giese-type coupling. This modification proved to be robust in larger scale (1.0 g) without the erosion of the yield (70%).



Entry	Substrate	Photocatalyst	Additives	Yield
1	12	P1	-	-
2	12	4CzIPN	-	-
3	12	Eosin Y	DIPEA (2.eq)	10%
4	12	HE	-	trace
5	7a	4CzIPN	Na_2CO_3 (0.2 eq)	-
6	7a	P1	Na_2CO_3 (0.2 eq)	-
7	7a	P1	Na_2CO_3 (0.2 eq), **bph** (1.0 eq)	29%
8	7a	DCA	K_2HPO_4 (0.15 eq), **bph** (2.0 eq)	36%
9	7a	Ir[df(CF3..]	K_2HPO_4 (0.15 eq), **bph** (2.0 eq)	-
10	7a	TBADT	K_2HPO_4 (0.15 eq), **bph** (2.0 eq)	-
11	7a	P1	K_2HPO_4 (0.15 eq), **bph** (2.0 eq)	55%
12	7a	P2	K_2HPO_4 (0.15 eq), **bph** (2.0 eq)	70%
13	7a	P3	K_2HPO_4 (0.15 eq), **bph** (2.0 eq)	8%
14	7a	P4	K_2HPO_4 (0.15 eq), **bph** (2.0 eq)	-

Scheme 5. Visible light mediated photo-redox decarboxylate Giese reaction.

After this successful photo-redox coupling, we aimed to screen the scope and limitation of this method. Thus, various Michael acceptors have been evaluated (Scheme 6). Gratifyingly, several β-unsubstituted and electron-deficient olefins proved to be efficient coupling partner in this reaction. Nevertheless, we found that β-substituted olefins are less efficient or even unproductive coupling partners in this decarboxylative route.

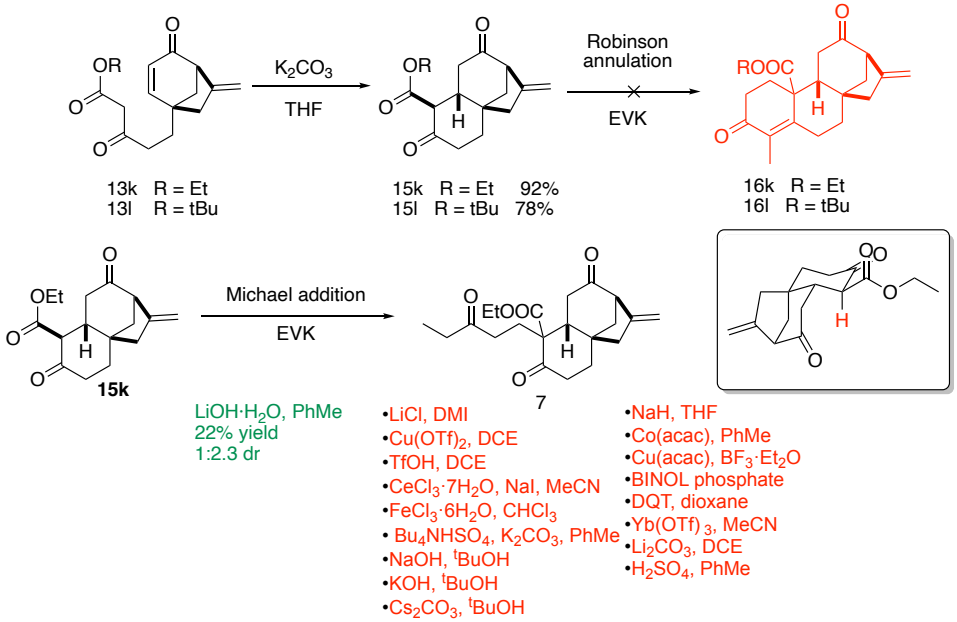


Scheme 6. Investigation of scope and limitations.

Finally, we investigated the requirement of the structural orthogonality of the radical in this reaction (see in Scheme 6). Using non-bridged analog system **14**, only decarboxylation and no C-C bond formation occurred, which might be the result of the formation of conjugated, allyl radical.

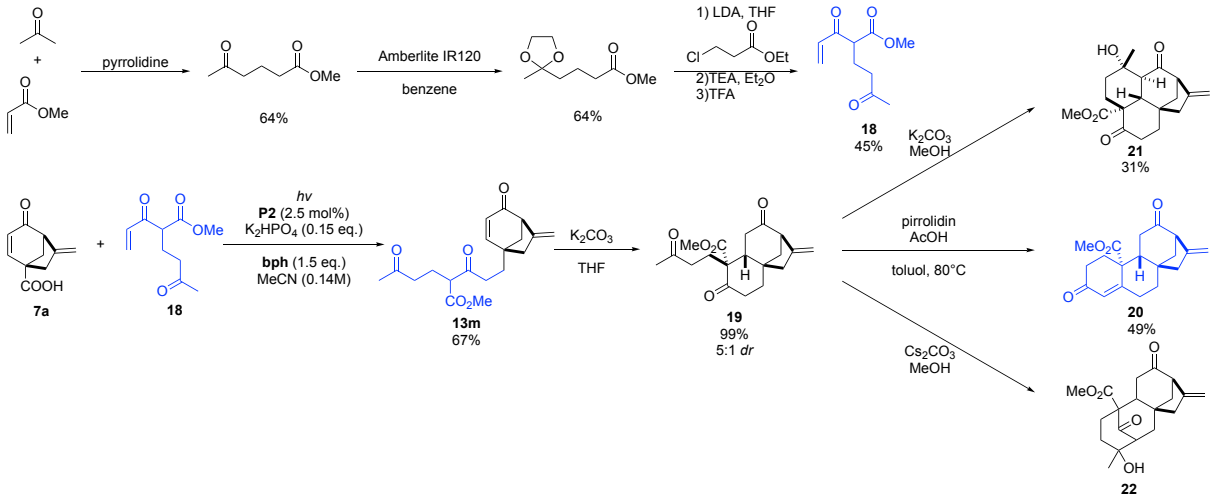
As the radical annulation proved to be unattainable on these coupled products, we focused on the ionic ring-closures (Scheme 7). Therefore, we targeted the envisioned annulation strategy using Nazarov's reagent. To our delight, after photoredox-coupling, we could affect a diastereoselective ring closure reaction using inorganic bases. Further elaboration of these structures **15k,l** toward a Robinson annulation products **16k,l** using ethyl vinyl ketone (**EVK**), however, proved to be impassable. Then various reagents, bases, Lewis acids and conditions have been tested, but even Michael adduct formation was problematic, only LiOH was able to deliver **17** adducts, and the minor diastereomer was that needed for our synthetic purposes. The mitigated reactivity of the **15** seems to have a sterical reason: the bulky ester moiety

occupies an equatorial position in **15k** and the introduction of the alkyl group in the axial position is hindered by dual syn-pentane strain.



Scheme 7. Further synthetic elaboration and investigation of Robinson annulation

This prompted us to develop an alternative tactic (Scheme 8). We envisioned that we should utilize a modified Nazarov's reagent **18** with a built-in Robinson annulation capacity. Using this reagent, not only a more convergent, but an enforced double-annulation route can be realized. Triggered by these options, we synthesized this modified Nazarov's reagent in a three-step route. Then, we could couple this advanced reagent with the bridged carbocylic building block **7a** in our photo-redox mediated reaction. To our delight, this coupled product **13m** could be annulated with high efficiency and diastereoselectivity to afford **19**. Next, the final ring closure was probed, however, we could not realize under basic conditions the targeted compound **20**. The envisioned Robinson annulation took different and surprising pathways, we could isolate the formation of rather unusual products **21** and **22**. Finally, after many experimentations, we found that pyrrolidinium acetate, a basically organocatalytic method can solve our problem as the desired product **20** was formed in a 49% yield. Thus, we accomplished the synthesis of the kaurene core with a correct stereochemistry.



Scheme 8. Successful double annulation tactics to afford kaurene core.

To sum up, we developed a novel route to construct highly functionalized kaurene core **20** in a rapid and convergent manner. This route based on a "iso-Diels-Alder" annulation strategy that we envisioned for this project and successfully realized. Additionally, we discovered that a modified Nazarov's reagent **18** should be implemented with a built-in Robinson annulation capacity to realize the synthesis of the kaurene structure. Our unique approach delivers many advances in the synthetic field including method developments and total synthesis. Our advances provide a (1) solution for annulation to bridgehead position, demonstrate (2) the first photo-redox mediated couplings, to best of our knowledge, between highly advanced reaction partners (both molecules are Michael acceptor) which can be elaborated further to annulation. While these advances can be published in highly prestigious journals such as Organic Letters or Chemistry a European Journal, our strategy to continue further this synthetic work to reach the level of Nature Chemistry. Accordingly, we (Kristóf Hegedüs, Bálint Kőnig and Gergely Répási) are currently pursuing to demonstrate that this approach is divergent and can deliver not only one, but several kaurene terpenoids. Accordingly, we are working on the end-game of selected total syntheses.

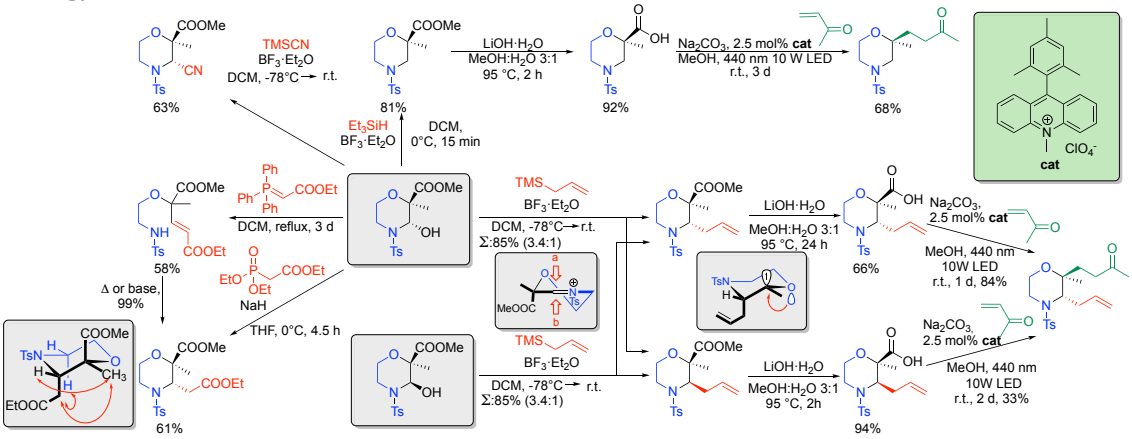
Spin off results

During this total synthesis endeavor, we encountered many synthetic problems, recognized possible applications, and made serendipitous discoveries. As a result, we accomplished further total syntheses, developed unique methods during the last 5 years. These efforts led to publications, patent, and unpublished works. In the following I summarize those activities:

1. *Visible light photo redox chemistry for morpholine synthesis*

When we recognized the broad utility and practicality of decarboxylative photo-redox chemistry, we aimed to expand this tool in the synthesis of highly decorated and

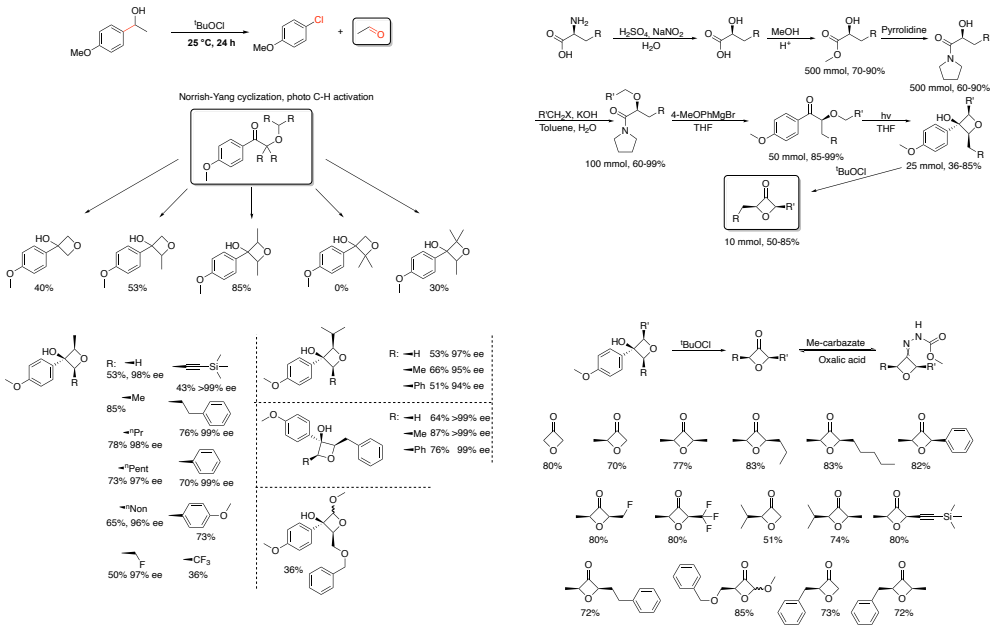
conformationally locked morpholines. This study was successful, a divergent and expedient synthetic method was developed (Scheme 9). Interestingly, the method is diastereoconvergent, the decarboxylative process proved to be deliver only one possible isomer owing to stereoelectronic effect. The manuscript (first author: Bálint Kőnig) is under evaluation at JOC.



Scheme 9. Summary for the synthesis of functionalized morpholines.

2. *Photochemistry in strained heterocycle synthesis*

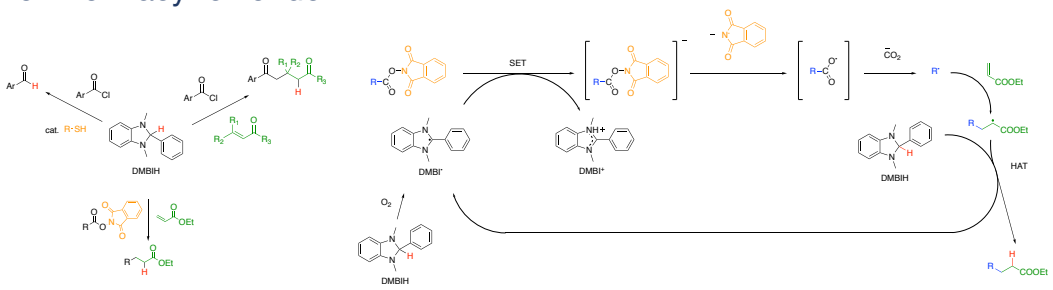
During our synthetic endeavor on oxidation protocols, we have discovered a unique retro-Friedel-Crafts reaction (Scheme 10). Using various benzylalcohol derivatives of anisoles, we have found a surprising C-C bond cleavage reaction by t-BuOCl (instead of the oxidation of the alcohol to ketone). This unique reactivity triggered us to exploit this chemistry further, more specifically toward strained heterocycles. Thus, we intertwined the Norrish-Yang photocyclization with oxidative fragmentation of the aromatic ring. As a result, a scalable and paractical route has been developed to chiral oxetanes. This chemistry may represent a significant advance in medicinal chemistry. The manuscript of this work is under preparation (first author: Kristóf Hegedüs) and expected to be submitted next year.



Scheme 10. Summary of intertwined Norrish-Yang photocyclization with oxidative retro-Friedel-Crafts reaction to access chiral oxetanones.

3. *Organoredox chemistry without light or thermal trigger. Single electron transfer methods*

In parallel, we developed a novel decarboxylative Michael addition protocol without the need of photo- or thermal radical initiation. This radical protocol employs a benzimidazoline-based organohydride reducing agent which can act as a SET initiator in the process (after reaction with trace amount of O_2). Owing to the novelty of this observation, we expanded our investigation of this unique reagent and discovered new, radical based acyl-chloride to aldehyde transformation (using thiol as a polarity-reversal catalyst) as well and radical, reductive Giese-type reaction from acyl-chloride.



Scheme 11. Summary of the mechanistic concept an application of DMBIH based radical couplings.

4. *Total synthesis of Aspidosperma alkaloids using advanced cyclohexanone building blocks*

During this research period, we embarked on the total synthesis of various Asidosperma alkaloids. We accomplished the total synthesis of five complex indole-terpenoids using a cyclohexanone building block with quaternary stereogenic center. The analogous building block **7a,b** was used in kaurene synthesis. Our manuscripts have been accepted in Angewandte Chemie and Organic Letters (see ref 6). These papers aroused a great interest, they were highlighted in Synfacts, became the most downloaded paper, cited even in the Youtube.

5. *Intertwining thianthrenium chemistry with Kornblum oxidation. A metal-free C–H activation method*

During the last period of our research, a widely applicable, practical, and scalable synthetic method for efficient ene-type double oxidation of alkenes was developed via a two-step alkenyl thianthrenium umpolung/ Kornblum-Ganem oxidation strategy. This chemo- and stereoselective procedure allows easy access to various α,β-unsaturated carbonyls that may be otherwise difficult or cumbersome to synthesize by conventional methods. For α-olefins, this metal-free transformation can be tuned according to synthetic needs to produce either the elusive (Z)-unsaturated aldehydes or their (E) counterparts. Moreover, this strategy has enabled streamlined synthesis of distinct butadienyl pheromones and kairomones. We submitted a provisional patent and our paper was accepted for publication in Angewandte Chemie as a “Hot Paper” this year.[11]

[11] Angyal, P., Kotschy, A. M., Dudás, Á., Varga, S., Soós, T. *Angew. Chem. Int. Ed.* 10.1002/anie.202214096.